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10/506,766	11/12/2004	Pascal Bigey	37991-0032	3543

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/506,766	BIGEY ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *4-6 and 17-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-16 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-1-2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Pending Claims

Applicant's election without traverse of claims 1-3, 7-16, and 29 pertaining to SEQ ID NO:1 in the reply filed on August 9, 2006 is acknowledged. Applicant has withdrawn claims 4-6 and 17-28 as well as SEQ ID NO:2 from further consideration in the reply filed on August 9, 2006. Accordingly, claims 1-29 are pending and claims 1-3, 7-16, and 29 pertaining to SEQ ID NO:1 are currently under examination.

Specification

The disclosure is objected to because of the following informalities: This application contains Drawings (Figures 1&2) that require brief description of drawings in the specification. See MPEP §608.01 and 37 CFR 1.74.

Appropriate correction is required.

Information Disclosure Statement

The information disclosure statement filed on December 1, 2005 has been placed in the application file, but the information referred to as Citation No. A03 (WO 99/01157 A1) has been considered as to the merits only as far as the English abstract.

Claim Objections

Claim 2 is objected to for containing non-elected subject matter. Appropriate correction is required.

Claim 16 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

As claimed, it is unclear whether the recited "bleomycin" in line 2 of claim 16 is distinct from the recited "compound belonging to the bleomycin family" in lines 2-3 of claim 3, because the instant specification does not disclose any members of bleomycin family except for bleomycin. Clarification is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7-16, and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a combination product comprising at least one MBD2 antisense oligonucleotide and bleomycin wherein administration of said antisense oligonucleotide occurs 30 minutes after the injection of bleomycin via electrotransfer carrying 500V/cm current for the treatment of proliferative disease, does not reasonably provide

enablement for a combination product comprising any other agents or any other routes of antisense administration with any other electric current strengths for the treatment of proliferative and inflammatory diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-3, 7-16, and 29 are drawn to a combination product for therapeutic use in eukaryotic cells *in vivo*, comprising MBD2 antisense oligonucleotide that is at least 15 consecutive nucleotides of SEQ ID NO:1 and an agent used in antitumor chemotherapy (claims 1-2 and 7-11), wherein said agent is bleomycin (claims 3 and 16) and said antisense oligonucleotide is electro-transferred (claims 12-15 and 29).

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Although the instant claims are not directed to methods of treating diseases, the instantly claimed combination products recited to be "intended for the treatment of proliferative and inflammatory diseases" (claim 1, lines 3-4). In light of the claim language imparted by such phrase, the instantly claimed invention is construed to mean pharmaceutical composition.

The instant specification does not disclose the nucleic acid sequence of the MBD2 antisense plasmid used in the examples 1.1-1.3 on pages 12-19. It discloses the quantity of the MBD2 antisense plasmid administered into mice; however, the "actual" identity of the MBD2 antisense plasmid construct that shows delayed tumor development in concert with bleomycin is undisclosed in the instant specification. Therefore, one skilled in the art cannot predict whether a random selection of any MBD2 antisense oligonucleotide comprising at least 15 consecutive nucleotides of SEQ ID NO:1 would result in an anti-tumor activity *in vivo*.

As neither antisense therapeutics nor clinical trials are performed routinely in the art, to determine whether pharmaceutical compositions comprising any region of SEQ ID NO:1 of any length would effectively treat proliferative and inflammatory diseases would require undue experimentation. The unpredictable therapeutic effects of DNA-based drugs for therapeutic use are addressed by Patil et al's comprehensive review (*The AAPS Journal,* 2005, 7:E61-E77).

On page E62, Patil et al. teach the complications of using DNA-based drugs as following:

"The innate ability of DNA-based drugs to be internalized by target cells is minimal under normal circumstances. In addition, poor biological stability and a short half-life result in unpredictable pharmacokinetics. Furthermore, DNA molecules that do manage to enter the cell are subsequently subjected to intracellular degradation along with stringently restricted nuclear access. The resulting random delivery profile of DNA-based drugs is further complicated by a lack of in vivo/in vitro correlation of their pharmacological outcomes."

In light of the above, it would have been unpredictable whether the claimed invention would have elicited successful inhibition of MBD2 function/expression, had any antisense oligonucleotides targeted to any portion more than or equal to 15 consecutive nucleotides in length of SEQ ID NO:1 been administered to an organism *in vivo* at the time the invention was made. In line with the teachings of Patil et al. that a clinical application of DNA-based drugs, such as antisense oligonucleotides of the instant application, requires careful series of trial and error tests for ensured success of bioavailability and pharmacokinetics of the DNA-based drugs due to "unpredictable pharmacokinetics" of internalized DNA-based drugs, one skilled in the art would not be able to determine whether the simultaneous or prolonged use of the combination product will result in the anti-cancer effect, because the instant specification exemplifies only one type of administration in which the MBD2 antisense construct is administered 30 minutes after bleomycin injection. Likewise, since the instant specification provides working examples only for electrotransfer administration of the antisense construct at a specific current, 500 V/cm, one skilled in the art can only rely on this specific method of administration. Since the invention is contingent on the unpredictable nature of DNA-based drugs, one skilled in the art cannot extrapolate that other means of antisense administration or electrotransfer with different electro-current other than 500 V/cm will render therapeutic effects *in vivo.* In view of the foregoing, the instant disclosure does not provide any guidance required to overcome the art-recognized unpredictability of using DNA-based drugs in therapeutic applications.

In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), the Court ruled that a rejection under 35 U.S.C. 112, first paragraph for lack of enablement was appropriate given the relatively incomplete understanding in the biotechnological field involved, and the lack

of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims. One skilled in the art cannot predict that the claimed combination product will be effective, if other than the MBD2 antisense plasmid exemplified in the instant specification is administered into mice *in vivo*. It is well known that the art of nucleic acid-based drug discovery for therapy is highly unpredictable as stated above. It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the combination product comprising an antisense oligonucleotide and an antitumor agent would be used without undue experimentation.

In light of the above, undue experimentation would have been needed to make and use the claimed invention based on the content of the disclosure (i.e., amount of direction and existence of working examples provided by the inventor) and the state of the prior art, the level of one of ordinary skill, and the level of predictability in the art. In view of all these factors and the totality of the teachings that the activity of DNA-based drugs are unpredictable *in vivo*, undue experimentation would be required of the skilled artisan to practice the instantly claimed invention, thus claims 1-3, 7-16, and 29 are not enabled.

Claims 1-3, 7-16, and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and /or chemical properties, functional characteristics, structure/function correlation, or any combination thereof.

The claims are drawn to combination products comprising at least one antisense oligonucleotide of the gene encoding MBD2 demethylase and at least one agent used in antitumor chemotherapy for the treatment of proliferative and inflammatory diseases.

As broadly claimed without a positive recitation of SEQ ID NO in claim 1 and its dependent claims, the recited antisense oligonucleotide reads on any portion, any size, any structure of the gene encoding MBD2 demethylase. In order to provide evidence of possession of such claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus as stated above. The instant specification discloses neither structure/function correlation nor complete or partial structure of the claimed genus. In fact, the specification is silent about any antisense oligonucleotide sequences or structures in the instant specification. Although claim 2 specifically recites "15 consecutive nucleotides of the sequence SEQ ID NO:1" in line 3, it fails to particularly point out the claimed invention because SEQ ID NO:1 comprises 1966 nucleotides and to choose any given region of at least 15 consecutive nucleotides as claimed does not significantly narrow the scope of the broad claim, claim 1. Similarly, the instant specification has not set forth all the classes of antitumor agent used in the treatment of proliferative and inflammatory disease. Since neither the specification nor the claims disclose any particular structure of the claimed antisense oligonucleotide, and since the "agent used in antitumor chemotherapy" embraces a myriad of agents while the specification and

the claims disclose enabled species of bleomycin, one skilled in the art cannot ascertain whether the inventor was in possession of the claimed invention.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991), which clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (see page 1117).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 7-16, and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "prolonged use" in claim 1, line3 and claim 14, line 2, is a relative term which renders the claim indefinite. The term "prolonged" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Since "prolonged" use reads on 1 week of use, 1 month of use, or 1 year of use, and so forth, the metes and bounds set forth by the term "prolonged use" are ambiguous thus rendering claims 1 and 14 as well as all their dependent claims indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 7-11, and 13-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Szyf et al. (US 2006/0166909 A1).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

The claims are drawn to combination products comprising an MBD2 demethylase antisense oligonucleotide of at least 15 consecutive oligonucleotides of SEQ ID NO:1 and an antitumor agent (claims 1-2), wherein the agent is bleomycin (claims 3 and 16), the antisense oligonucleotide is in a vector comprising a promoter (claim 7), a poly A transcription termination sequence (claim 8), the vector is a plasmid (claim 9), the oligonucleotide is double-stranded (claim 10), further comprises one or more elements promoting the transfer of the antisense oligonucleotide (claim 11), one or more pharmaceutically acceptable carrier (claim 13), for treatment of cancer (claim 14) and suitable for intratumor injection (claim 15).

Szyf et al. teach a combination product comprising a therapeutically effective amount of one or more oligonucleotides targeted to MBD2 demethylase and one or more anti-cancer

therapeutics that is bleomycin for treatment of cancer (paragraphs 0006 and 0113). They teach an antisense oligonucleotide comprising SEQ ID NO:12, which corresponds to 20 consecutive nucleotides of the instant SEQ ID NO:1 from nucleobase 815 to 834. They teach that this antisense oligonucleotide can be sincle-stranded or double-stranded (paragraph 0045) and that it can be inserted into an expression vector that is a plasmid and having regulatory elements such as promoters and polyadenylation signals (paragraphs 0088-0089 and 0134). They teach that the oligonucleotide composition further comprises a pharmaceutically acceptable formulations for *in vivo* intratumor administration (paragraphs 0125-0133). Szyf et al. show inhibition of tumor cell growth *in vivo* by antisense oligonucleotide inhibitors comprising SEQ ID NO:12 (also identified as A10). See Examples 5-6.

Accordingly, all the structural limitations of the instantly claimed invention are met by Szyf et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 7-16, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slack et al. (*The Journal of Gene Medicine,* 4:381-389, published online May 17, 2002, applicant's Citation No. A06, Form PTO/SB/08A filed on December 1, 2005) in view of Wang et al. (*Clinical Cancer Research,* 2001, 7:3613-3624).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

The claims are drawn to combination products comprising antisense oligonucleotide targeted to MBD2 demethylase and an antitumor agent that is bleomycin, wherein the antisense oligonucleotide is suitable for *in vivo* electrotransfer by weak electric fields of between 1 and 600 V/cm.

Slack et al. teach an antisense MBD2 construct that results in reduced tumorigenesis in mice *in vivo,* wherein the antisense construct is administered via electrotransfer at 500 V/cm (page 385-388). They teach that MBD2 is a potential anticancer target. See last paragraph of the Discussion section on page 388. Slack et al. do not teach a combination product comprising an antisense MBD2 construct and bleomycin.

Wang et al. teach that administration of an MDM2 antisense oligonucleotide in combination with an anti-cancer chemotherapeutics such as 5-fluorouracil, irinotecan, and

paclitaxel results in significant synergistic anti-cancer effects *in vivo* (pages 3618-3619 and Table 1). They teach that bleomycin is a commonly used anti-cancer agent (page 3613).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a combination product comprising an MBD2 demethylase antisense oligonucleotide and an anti-tumor agent, which is bleomycin. One of ordinary skill in the art would have been motivated to combine the teachings of the prior art with a reasonable expectation of success because Slack et al. teach the pharmaceutical efficacy of MBD2 antisense in reducing tumorigenesis *in vivo* and because Wang et al. teach the supra-additive therapeutic effect of combining antisense oligonucleotides with generic chemotherapeutic agents, one of which is bleomycin. Further, the skilled artisan would have been motivated to practice the invention via a specific type of route of administration of the MBD2 antisense construct by electro-transferring the construct at 500 V/cm with a reasonable expectation of success, because Slack et al. specifically teach successful reduction of tumorigenesis *in vivo* via electrotransfer of the MBD2 antisense construct at 500 V/cm. Accordingly, in view of the prior art, the invention taken as a whole would have been *prima facie* obvious at the time the invention was made.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635